STATISTICAL ANALYSIS PLAN

402-C-2002

VERSION: 2.0

DATE OF PLAN:

06-Oct-2021

BASED ON:

Protocol Version 2.0 – 17 Feb 2021

STUDY DRUG:

RTA 402, BARDOXOLONE METHYL

PROTOCOL NUMBER:

402-C-2002

STUDY TITLE:

A phase 2 trial to evaluate safety, tolerability, and efficacy of Bardoxolone Methyl in patients with chronic kidney disease at risk of rapid progression

SPONSOR:

Reata Pharmaceuticals, Inc.

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TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company: **Reata Pharmaceuticals, Inc.**	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: Bardoxolone methyl capsules	**Page:**	
Name of Active Ingredient: Bardoxolone methyl		
Title of Study: A phase 2 trial to evaluate safety, tolerability, and efficacy of Bardoxolone Methyl in patients with chronic kidney disease at risk of rapid progression		
Investigators: Study Center(s): 11 Sites used		
Studied period (years): Estimated date first patient enrolled: December 2020 Estimated date last patient completed: July 2021	**Phase of development: 2**	

Objectives:

Primary:

- To assess the change from baseline in estimated glomerular filtration rate (eGFR) at Week 12
- To assess the safety and tolerability of bardoxolone methyl

Secondary:

- To characterize the eGFR response at Week 12 across different etiologies of Chronic Kidney Disease

Exploratory:

- To characterize change in eGFR during the off-treatment period
- [redacted]

Methodology:

This multi-center, randomized double-blind, placebo-controlled, Phase 2 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with CKD due to multiple etiologies at risk of rapid disease progression. Approximately 70 patients will be enrolled and randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified using the Kidney Disease: Improving Global Outcomes (KDIGO) CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) based on screening eGFR and UACR using Randomization and Trial Supply Management (RTSM).

Trial design includes screening, treatment period, and off-treatment period (OT).

Screening period: Includes 2 visits (Screen A and Screen B), and the duration of screening (from Screen A to Day 1) may not exceed 4 weeks. The Screen A and B visits may be completed on consecutive days.

Treatment period (Day 1 through Week 12): Includes 13 visits (clinic and phone visits). Patients who successfully meet the enrollment criteria will be randomized using RTSM. Post randomization study drug will be dispensed accordingly. Day 1 of the treatment period is the day of randomization.

The maximum bardoxolone methyl dose will be determined by baseline proteinuria status. Patients with baseline urine albumin to creatinine ratio (UACR) $\leq$ 300 mg/g will be titrated to a maximum dose of 20 mg, and patients with baseline UACR > 300 mg/g will be titrated to a maximum dose of 30 mg.

Qualified patients will be randomized 1:1 to receive either bardoxolone methyl or placebo once daily (preferably in the morning) throughout a 12-week dosing period. Randomization will be stratified using the KDIGO CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) based on screening eGFR and UACR using RTSM. Patients randomized to bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline UACR > 300 mg/g) unless contraindicated clinically, which should be discussed with the medical monitor. Patients randomized to placebo will remain on placebo throughout the study and will follow the same titration to maintain the blind. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted to meet the dosing objective of the highest tolerated dose.

Patients in the study will follow the same visit and assessment schedule. Patients will be assessed during treatment at Day 1, Weeks 1, 2, 4, 6, 8, and 12, and by telephone contact on Days 3, 10, 21, 31, 35, and 45. Date of last dose and the end-of-treatment assessments mark the end of the treatment period. Patients will not receive study drug during a 5-week off-treatment period between Weeks 12 and 17.

Off-treatment period (OT): Includes 5 visits requiring various assessments to characterize eGFR from the time of study drug discontinuation through Day 35 off-treatment. Patients will be assessed on Day 3 OT, Day 7 OT, Day 14 OT, Day 21 OT, Day 28 OT, and Day 35 OT. The OT day corresponds to days after last dose. Day 1 OT is the first day after receiving the last dose. Any patient who permanently discontinues study treatment early will follow the same OT assessment schedule.

End-of-study (EOS): All patients, including patients who discontinue treatment early, should complete the EOS visit 17 weeks after randomization.

Number of Subjects (planned and analyzed):

Approximately 70 patients will be enrolled.

Diagnosis and main criteria for inclusion

Inclusion criteria:

1. Male and female patients 18 ≤ age ≤ 75 upon study consent;
2. Diagnosis of CKD with screening eGFR (average of Screen A and Screen B eGFR values) ≥ 20 to < 60 mL/min/1.73 m^2
   a. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have a percent difference ≤ 25%;
3. Patient must meet at least one of the following criteria:
   a. UACR ≥ 300 mg/g; OR
   b. eGFR decline at a rate of ≥ 4 mL/min/1.73 m^2 in prior year; OR
   c. Hematuria (glomerular) defined as > 5-10 red blood cells (RBCs) per high power field (HPF, manual method), or documented history of positive urinary dipstick for blood in prior year, or macroscopic hematuria in prior 3 years;
4. Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at Screen A or Screen B visit after a period of rest (≥ 5 minutes);
5. Treatment with an angiotensin-converting enzyme inhibitor (ACEi) and/or an angiotensin II receptor blocker (ARB) at the maximally tolerated labeled daily dose for at least 6 weeks prior to the Screen A visit and with no anticipated changes to dose(s) during study participation. If treatment with ACEi and/or ARB is contraindicated or not indicated, the patient must not have been exposed to an ACEi and/or ARB for at least 8 weeks prior to the Screen A visit;
6. Absolute neutrophil count > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin (Hgb) ≥ 8.0 g/dL;
7. Total bilirubin (TBL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 1.5X the upper limit of normal (ULN) both at Screen A and Screen B visits;
8. Able to swallow capsules;
9. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
10. Evidence of a personally signed and dated informed consent document indicating the patient has been informed of all pertinent aspects and risk of the study prior to initiation of any protocol-mandated procedures.

Exclusion criteria:

1. Prior exposure to bardoxolone methyl;
2. CKD secondary to or associated with any of the following:
   a. History of rapidly progressive glomerulonephritis (RPGN)
   b. Glomerulonephritis requiring immunosuppression in the last 6 months prior to Screen A;
3. Concomitant use of tolvaptan. Patients previously treated with tolvaptan must have discontinued drug for at least 3 months prior to Screen A visit;
4. Patients treated with polycystic kidney disease-modifying agents (somatostatin analogues) within 3 months prior to the Screen A visit;
5. Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to Day 1 or anticipated need for immunosuppression during the study;

6. Patients currently taking a sodium/glucose cotransporter-2 inhibitor (SGLT2i), requiring dose adjustments within 12 weeks prior to Day 1 or if dose is anticipated to change during study participation;
7. B-type natriuretic peptide (BNP) level > 200 pg/mL at Screen A visit;
8. Uncontrolled diabetes (HbA1c > 11.0%) at Screen A visit;
9. Serum albumin < 3 g/dL at Screen A visit;
10. Kidney or any other solid organ transplant recipient or a planned transplant during the study;
11. Acute dialysis or acute kidney injury within 12 weeks prior to Screen A visit or during Screening;
12. History of clinically significant cardiac disease, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease
    b. Left ventricular ejection fraction < 40% (based on historical echocardiogram)
    c. History of hospitalization for heart failure within 12 months prior to Screen A
    d. New York Heart Association Class III or IV congestive heart failure (CHF)
    e. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or unstable angina) within 12 months prior to Screen A
    f. Pericardial constriction (based on historical echocardiogram)
    g. Restrictive or congestive cardiomyopathy (based on historical echocardiogram)
    h. Uncontrolled atrial fibrillation
    i. History of unstable arrhythmias;
13. Systolic blood pressure < 90 mmHg at Screen A visit after a period of rest;
14. Body mass index < 18.5 kg/m2 at the Screen A visit;
15. History of malignancy within 5 years prior to Screen A visit, with the exception of localized skin or cervical carcinomas;
16. Coronavirus disease 2019 (COVID-19) diagnosis within 3 months prior to Screen A or have ever required COVID-19 related hospitalization;
17. Participation in other interventional clinical studies within 3 months (or if relevant 5 half-lives of that study medication, whichever is the longer) prior to Screen B;
18. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested;
19. Women who are pregnant or breastfeeding;
20. Need for ongoing use of strong and/or moderate CYP3A4 inhibitors and inducers;
21. Known hypersensitivity to any component of the study drug;
22. Patient is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason.

Test product, dose and mode of administration:
Bardoxolone methyl at 5, 10, 20 or 30 mg will be administered orally once daily through Week 12.

Duration of treatment:
Bardoxolone methyl will be administered once daily through Week 12.

Reference therapy, dose and mode of administration:
Matching placebo will be administered orally once daily through Week 12.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: eGFR change from baseline at Week 12.

Secondary efficacy endpoint: eGFR change from baseline at Week 12 by CKD etiology.

Exploratory efficacy endpoint: eGFR change from baseline at off-treatment Days 3, 7, 14, 21, 28, and 35.

Safety:

Laboratory results (clinical chemistry, hematology, urinalysis, and microscopy), vital sign measurements, electrocardiogram (ECG) results, weight, adverse events (AEs), and serious adverse events (SAE).

Other endpoints:

[redacted]

Statistical methods:

Sample size:

[redacted]

Analysis of the primary endpoint will be based on the intent-to-treat (ITT) population and analyzed using mixed-model repeated measures (MMRM) with an unstructured covariance structure [redacted] Appropriate sensitivity analyses of the primary analysis will be specified in the Statistical Analysis Plan (SAP). The secondary efficacy endpoint will be tested for sufficiently large subgroups, but the study is not powered to show efficacy in the secondary efficacy endpoint.

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Table 1: List of Abbreviations

Abbreviation	Term
ACEi	Angiotensin converting enzyme inhibitor
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
BMI	Body mass index
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations (US)
CHF	Congestive heart failure
CK	Creatine kinase
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
ESKD	End stage kidney disease
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HbA1c	Hemoglobin A1c
HDPE	High-density polyethylene
Hgb	Hemoglobin

Abbreviation	Term
HGVS	Human Genome Variation Society
HPF	High power field
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
KDIGO	Kidney Disease: Improving Global Outcomes
Keap1	Kelch-like ECH associated protein-1
Kf	Ultrafiltration coefficient
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MTLDD	Maximally tolerated labeled daily dose
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2
NT-ProBNP	N-Terminal Pro-Brain Natriuretic Peptide
OT	Off-treatment
PBO	Placebo
PH	Pulmonary hypertension
PK	Pharmacokinetic
PT	Prothrombin Time
QTc	Corrected QT interval
RBC	Red blood cell
RPGN	Rapidly progressive glomerulonephritis
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SGLT2i	Sodium/glucose cotransporter-2 inhibitor

Abbreviation	Term
SNGFR	Single nephron glomerular filtration rate
SOP	Standard operating procedure
T2D	Type 2 diabetes
TBL	Total bilirubin
UACR	Urine albumin to creatinine ratio
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1. Trial Rationale

Bardoxolone methyl is a semi-synthetic triterpenoid that selectively and reversibly binds to Kelch-like ECH-associated protein 1 (Keap1), resulting in potent activation of the transcription factor nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2). Through activation of Nrf2, bardoxolone methyl modulates the transcription of hundreds of genes involved in inflammation, oxidative stress, and cellular energy metabolism (Kobayashi, 2016; Wardyn, 2015).

Data from multiple animal models of chronic kidney disease (CKD) demonstrate that bardoxolone methyl and closely related structural analogs suppress inflammation and fibrosis, reduce glomerulosclerosis, prevent tubulointerstitial damage, and improve kidney function (Aminzadeh, 2014; Nagasu, 2019; Zoja, 2010). Additional studies have demonstrated that acute treatment with bardoxolone methyl reverses endothelial dysfunction and mesangial cell contraction, increases glomerular surface area (ultrafiltration coefficient, K_f), and restores single nephron glomerular filtration rate (SNGFR) without changes in intraglomerular pressure (Ding, 2013; Kidokoro, 2019).

In multiple clinical studies, treatment with bardoxolone methyl has consistently improved kidney function as assessed by either inulin clearance, creatinine clearance, or estimated glomerular filtration rate (eGFR) (Chin, 2018; de Zeeuw, 2013; Nangaku, 2020; Pergola, 2011). The increases in eGFR with bardoxolone methyl observed within the first 12 weeks of treatment have been shown to significantly correlate with longer-term changes in eGFR (Chin, 2018).

Moreover, in multiple, long-term clinical studies, the treatment effect relative to placebo has been shown to persist approximately four weeks after cessation of drug (de Zeeuw, 2013; Chin, 2018, Pergola, 2011). These results are thought to reflect the drug's anti-fibrotic effects and are consistent with beneficial effects on structural remodeling observed in animal models.

The assessment of eGFR during the off-treatment (OT) period is used to assess bardoxolone methyl's effect on the irreversible loss of kidney function as well as any disease modifying effects. Available clinical pharmacodynamic and pharmacokinetic data with bardoxolone methyl suggest that acute effects on eGFR are expected to resolve within 10 to 14 days after stopping treatment. In the present study, eGFR will be assessed at multiple intervals during the OT period to characterize the timecourse of the washout of bardoxolone methyl's acute pharmacodynamic effects.

Patients with CKD with rapid progression or at risk of rapid progression are defined as those with a sustained decline in eGFR of more than 4 to 5 mL/min/1.73 m^2 per year (KDIGO, 2013). The collective clinical and nonclinical data suggest that bardoxolone methyl may be effective at ameliorating the rate of decline in eGFR in this patient population. Furthermore, increases in eGFR observed after 12 weeks of treatment may translate to a sustained eGFR response. In patients with CKD at risk of rapid progression, the potential impact of a sustained eGFR increase with bardoxolone methyl treatment may be clinically meaningful and could translate to a delay in progression to end stage kidney disease (ESKD).

1.2. Background

The original study protocol has undergone the following amendment.

Protocol Revision Chronology:		
Protocol	18-NOV-2020	Original
Protocol Version 2	17-FEB-2021	Amendment 1

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to unblinding of the study data as described in Section 5.1. Further information can be found in the protocol.

The SAP is based on:

- Protocol 402-C-2002, Version 2.0, dated 17-FEB-2021
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)

This SAP describes the study populations, how variables are derived, how missing data are handled, and details concerning the statistical methods to be used to analyze the safety and efficacy data from Study 402-C-2002. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To assess the change from baseline in estimated glomerular filtration rate (eGFR) at Week 12.
- To assess the safety and tolerability of bardoxolone methyl.

2.1.2. Secondary Objective

- To characterize the eGFR response at Week 12 across different etiologies of Chronic Kidney Disease (CKD).

2.1.3. Exploratory Objectives

- To characterize change in eGFR during the off-treatment period.
- [redacted]

2.2. Study Endpoints

The study will compare those receiving bardoxolone methyl to those receiving placebo with respect to several endpoints. The timing for analyzing study endpoints is described in Section 5.5. Primary efficacy analyses are described in Section 7, and additional exploratory efficacy analyses are described in Section 8.

2.2.1. Primary Efficacy Endpoint

- eGFR change from baseline at Week 12.

2.2.2. Secondary Efficacy Endpoint

- eGFR change from baseline at Week 12 by CKD etiology.

2.2.3. Exploratory Efficacy Endpoint

- eGFR change from baseline at off-treatment Days 3, 7, 14, 21, 28, and 35.

2.2.4. Safety Endpoints

- Laboratory results (clinical chemistry, hematology, urinalysis, and microscopy), vital sign measurements (weight only), electrocardiogram (ECG) results, adverse events (AEs), and serious adverse events (SAEs).

2.2.5. Other Endpoint

- [redacted]

3. STUDY DESIGN

3.1. Summary of Study Design

This multi-center, randomized, double-blind, placebo-controlled, Phase 2 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with CKD due to multiple etiologies at risk of rapid disease progression. Approximately 70 patients will be enrolled and randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified using the Kidney Disease: Improving Global Outcomes (KDIGO) CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) (Section 19, Levin, 2014) based on screening eGFR and UACR using Medidata Randomization and Trial Supply Management (RTSM).

Patients with CKD secondary to varying etiologies will be enrolled from age 18-70 years with eGFR $\geq$ 20 to < 60 mL/min/1.73 m^2, and other risk factors for rapid progression of kidney disease. Patients with glomerulonephritis requiring immunosuppressive treatment within 6 months or a history of rapidly progressive glomerulonephritis will be excluded. No single CKD etiology ((hypertensive, diabetic, or other) may enroll approximately $\geq$ 40% in the trial.

The maximum target dose will be determined by baseline proteinuria status. Patients with baseline urine albumin to creatinine ratio (UACR) $\leq$ 300 mg/g will be titrated to a maximum dose of 20 mg, and patients with baseline UACR > 300 mg/g will be titrated to a maximum dose of 30 mg. Qualified patients will be randomized 1:1 to receive either bardoxolone methyl or placebo once daily (preferably in the morning) throughout a 12-week dosing period. Patients will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline UACR > 300 mg/g), unless contraindicated clinically, which should be discussed with the medical monitor (Figure 1). Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted to meet the dosing objective of the highest tolerated dose.

Patients in the study will follow the same visit and assessment schedule. Patients will be assessed during treatment at Day 1, Weeks 1, 2, 4, 6, 8, and 12 and by telephone contact on Days 3, 10, 21, 31, 35, and 45. Date of last dose and the end-of-treatment assessments mark the end of the treatment period. Patients will not receive study drug during a 5-week off-treatment period between Weeks 12 and 17 (Figure 1).

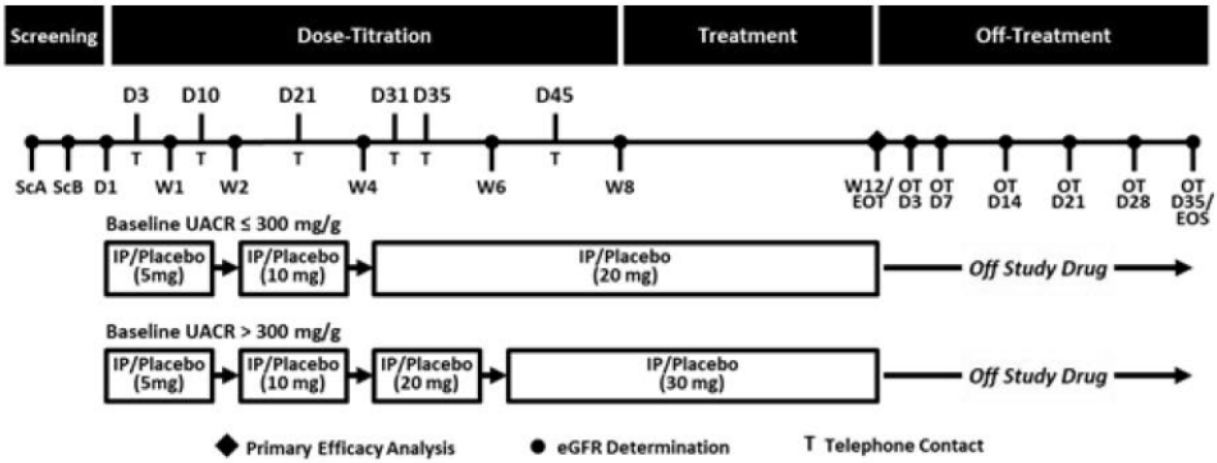
The off-treatment (OT) period includes 5 visits requiring various assessments to characterize eGFR from the time of study drug discontinuation through Day 35 off-treatment. Patients will be assessed on Day 3 OT, Day 7 OT, Day 14 OT, Day 21 OT, Day 28 OT, and Day 35 OT. The OT day corresponds to days after last dose. Day 1 OT is the first day after receiving the last dose. Any patient who permanently discontinues study treatment early will follow the same OT assessment schedule.

All patients, including patients who discontinue treatment early, should complete the end-of-study (EOS) visit 17 weeks after randomization.

All efforts should be made to follow all randomized patients for the full OT period of the trial, and the EOS visit (Week 17), including patients who discontinue drug early.

Final analysis of the primary efficacy endpoint will occur after all enrolled patients have completed their Week 17 visit (or have terminated from the trial).

Figure 1: Schema for Study 402-C-2002



Sc=Screening, UACR=urine albumin to creatinine ratio, eGFR=estimated glomerular filtration rate, EOT=end of treatment, EOS=end of study, OT=off-treatment period.

3.2. Definition of Study Drugs

Bardoxolone Methyl 5 mg and 15 mg capsules will be used. The matching placebo capsules will have the same appearance as the active doses.

3.3. Sample Size Considerations

[redacted]

3.4. Randomization

Qualified patients will be randomized 1:1 to bardoxolone methyl or placebo at Day 1 using RTSM. Randomization will be stratified using the KDIGO CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) based on screening eGFR and UACR using RTSM (KDIGO 2012; Levin, 2014).

Figure 2: Prognosis of CKD by eGFR and Albuminuria Categories

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30 – 300 mg/g 3 – 30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60 – 89			
	G3a	Mildly to moderately decreased	45 – 59			
	G3b	Moderately to severely decreased	30 – 44			
	G4	Severely decreased	15 – 29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.

3.5. Clinical Assessments

Patients in the study will follow the same visit and assessment schedule. Patients will be assessed during treatment at Day 1, Weeks 1, 2, 4, 6, 8, and 12, and by telephone contact on Days 3, 10, 21, 31, 35, and 45. Date of last dose and the end-of-treatment assessments mark the end of the treatment period. Patients will not receive study drug during a 5-week off-treatment period between Weeks 12 and 17.

Table 2: Schedule of Assessments

Assessments	Screening		Treatment Period												EOT	Off-Treatment Period (Based on Date of Last Dose)					EOS[a]
	Screen A[b]	Screen B[b]	Day 1[c]	Day 3 Day 3 ±2	Wk 1 Day 7 ±3	Day 10 Day 10 ±2	Wk 2 Day 14 ±3	Wk 3 Day 21 ±2	Wk 4 Day 28 ±3	Day 31 Day 31 ±2	Wk 5 Day 35 ±2	Wk 6 Day 42 ±3	Day 45 Day 45 ±2	Wk 8 Day 56 ±3	Wk 12[a] Day 84 –3	OT Day 3 +1	OT Day 7 ±2	OT Day 14 ±3	OT Day 21 ±3	OT Day 28 ±3	OT Day 35 –3 Week 17
Visit Method	Clinic	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Phone	Clinic	Phone	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Informed consent	X																				
Inclusion/ exclusion	X		X[d]																		
Demographics and baseline disease characteristics	X																				
Medical history	X																				
Collect CKD etiology	X																				
Height	X																				
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE collection			X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight in clinic	X		X		X		X		X			X		X	X						X
Weight at home[f]			X	X	X	X	X	X	X	X	X	X	X	X	X						
Dispense weight and IP diary			X				X		X			X		X							
Collect/review weight and IP diary				X	X	X	X	X	X	X	X	X	X	X	X						
ECG	X														X						X
Vital sign measurements	X[g]		X		X		X		X			X		X	X						X
Physical exam	X																				X
Targeted physical exam[h]			X		X		X		X			X		X	X						
Pregnancy test for WOCBP[i]	X	X	X		X		X		X			X		X	X						X
Study drug administration			----------X----------																		
Dispense study drug			X				X		X			X		X							
Collect/review study drug							X		X			X		X	X						
[redacted]			X																		
Clinical chemistry (incl. eGFR)	X	X	X		X		X		X			X		X	X	X	X	X	X	X	X
BNP and NT-proBNP	X		X		X		X		X			X		X	X						X
Hemoglobin A1c	X														X						
Hematology	X		X		X		X		X			X		X	X						X
Urinalysis and microscopy	X		X		X		X		X			X		X	X						X
Urine collection for UACR[k]		X							X					X	X						X
PK samples[l]															X	X	X	X	X	X	X

Assessments	Screening		Treatment Period												EOT	Off-Treatment Period (Based on Date of Last Dose)					EOS[a]
	Screen A[b]	Screen B[b]	Day 1[c]	Day 3 Day 3 ±2	Wk 1 Day 7 ±3	Day 10 Day 10 ±2	Wk 2 Day 14 ±3	Wk 3 Day 21 ±2	Wk 4 Day 28 ±3	Day 31 Day 31 ±2	Wk 5 Day 35 ±2	Wk 6 Day 42 ±3	Day 45 Day 45 ±2	Wk 8 Day 56 ±3	Wk 12[a] Day 84 −3	OT Day 3 +1	OT Day 7 ±2	OT Day 14 ±3	OT Day 21 ±3	OT Day 28 ±3	OT Day 35 −3 Week 17
Liver and Kidney Injury Biomarkers			X									X			X						X
C-Reactive Protein			X									X			X						X
PT/INR			X									X			X						X

[a] If a patient permanently discontinues study drug early, the patient should return as soon as possible to complete EOT procedures (i.e., those outlined at the Week 12 visit). The OT visits should then be scheduled based on the date of the last dose of study drug. Following completion of the OT visits, the EOS visit will occur at Week 17. In this case, there will be both an OT Day 35 visit scheduled 35 days following the last dose of IP and an EOS visit scheduled approximately 17 weeks after Day 1/randomization.

[b] Total Screening period should not exceed 4 weeks.

[c] Day 1 is administration of the first dose. **On Day 1, all procedures must be performed before study drug administration.**

[d] Screening eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures, and a urine pregnancy test should be performed for WOCBP.

[e] AE assessments on Day 1 should be performed following study drug administration.

[f] Weights should be taken at the same time each day and recorded in a patient diary. During the first eight weeks, weights will be recorded daily; weekly weights will be recorded from Week 8 through Week 12.

[g] Blood pressure for inclusion criteria eligibility can be taken at Screen A or Screen B. Blood pressure should not be collected at Screen B if Screen A values met eligibility criteria.

[h] Investigator should evaluate if a targeted physical exam is needed, based on any symptomatology reported to the study team.

[i] A serum pregnancy test will be performed at the Screen A visit for WOCBP or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs/ECs.

[redacted]

[k] Urine albumin to creatinine ratio will be measured by first morning void spot urine collection. Containers for the collection will be provided to the patient at the visit prior to the collection.

[l] Patients must not take study drug on the day of the Week 12 visit since PK will be drawn.

4. PLANNED ANALYSES

4.1. Final Analyses

The final analyses of efficacy will be based on locked data and performed after all enrolled patients have completed all efficacy assessments and data are unblinded. Unblinding will occur according to Standard Operating Procedure (SOP) BI-040.The final analyses of safety will be based on locked data and performed after all enrolled patients have completed all safety assessments and data are unblinded.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

The efficacy and safety analyses use the analysis sets defined in Section 5.3. Patient listings (as appropriate) of all analysis data that support summary tables and/or figures are provided along with their source data. The summary tables do not include measurements from patients excluded from the pre-defined analysis sets or extra measurements, such as values not closest to the target study day unless specified otherwise, but the patient listings do include these data. Missing data are not imputed, unless otherwise specified. In general, patient listings are sorted by patient number and assessment date (time and parameter, as applicable). Any laboratory value (including eGFR), vital sign assessment, or ECG value collected after starting dialysis or after receiving a kidney transplant is considered invalid and will be treated as missing. If a subject has a moderate, severe or serious adverse event of COVID, all safety and efficacy findings except AEs in both the on-treatment and off-treatment periods will not be summarized after the start date of the COVID adverse event start date.

5.1. General Summary Table and Individual Subject Data Listing Considerations

Results of statistical analyses are reported using summary tables, listings, and figures (TLFs). All TLFs will use ICH numbering conventions. For endpoints not described in Section 7.4, the reported significance levels are nominal, and the following statistical conventions are used:

- Unless otherwise noted, all statistical testing is two-sided and is performed at the 0.05 significance level.
- Tests are declared statistically significant if the calculated p-value is <0.05.

5.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Unless otherwise specified, descriptive statistics for continuous variables include the number of patients with data (N), mean, standard deviation (SD), median, minimum, and maximum. The same number of decimal places as in the observed value are presented when reporting minimum and maximum; 1 more decimal place than in the observed value is presented when reporting mean and quartiles; and 2 more decimal places than in the observed value is presented when reporting SD.

Categorical data are presented using frequency counts and percentages. All percentages are rounded to 1 decimal place, unless otherwise specified. Percentages equal to 100 are presented as 100% and no percentages are presented for zero frequencies. Where individual variable values are missing, summaries of categorical data are based on reduced denominators (i.e., the denominators include only patients with available data) and the number of missing values is presented. For summaries of AEs and concomitant medications (CM), the percentages are based on the total number of patients in each treatment group.

5.3. Analysis Populations

Analysis populations defined in this section pertain to patients enrolled in the MERLIN study.

5.3.1. ITT Population

The intent-to-treat analysis set is defined as all enrolled patients categorized by their randomized treatment group (whether or not they received study drug). The primary analysis population for the primary and key secondary efficacy endpoints is the ITT population.

5.3.2. Safety Population

Safety analyses are based on all enrolled patients. The safety population includes all patients who received at least 1 dose of study drug. The safety population is used for evaluation of safety variables. Patients who received at least one dose of bardoxolone methyl will be classified in the bardoxolone methyl group. Patients who received at least one dose of placebo and no dose of bardoxolone methyl will be classified in the placebo group.

5.4. Baseline Definition

Below is a summary of baseline value calculations. If the first study drug administration occurs after the date of randomization, the last measurement prior to the first study drug administration is considered the Day 1 measurement for the calculation of baseline.

Assessments without timestamp collected on the same date as the first date of study drug administration are considered to occur before the first dose of study drug administration.

This baseline value will be used for both On-Treatment and Off-Treatment analyses.

5.4.1. Baseline Age

Baseline age is defined as the age at consent (Screen A).

5.4.2. Estimated Glomerular Filtration Rate

Baseline eGFR is defined as the average of screening and Day 1 eGFR measurement, calculated as shown below:

- Screening eGFR = average of the last two eGFR measurements collected prior to the Day 1 eGFR collection
- Day 1 eGFR = the measurement after screening but on or before the date of first study drug administration
- Baseline eGFR = (0.5 × Day 1 eGFR) + (0.5 × Screening eGFR)

If there are only 2 observations available, then the average of the 2 values is used as baseline.

5.4.3. Serum Creatinine

Baseline serum creatinine (SCr) is defined in the same way as baseline eGFR (Section 5.4.2)

5.4.4. Urine Albumin to Creatinine Ratio

Baseline UACR is defined as the last value - collected prior to the study drug administration.

5.4.5. Safety Assessments

Baseline for continuous safety assessments (i.e., vital sign assessments - weight, BMI, and laboratory measurements) is defined as the average value of measurements collected up through the date of, but not after, first study drug administration. When three blood pressure measurements are taken on one visit, the average of the second and third measurement will be used for the aforementioned visit.

For all other situations not described above, baseline values are to be defined as the last non-missing assessment prior to the first study drug administration, unless otherwise specified below.

5.5. Derived and Transformed Data

5.5.1. Study Day

Study day is the day relative to the date of randomization. Day 1 is defined as the date of randomization. Assessments that occur after randomization but before the first dose of study drug are considered to occur on study Day 1.

Assessments without timestamp collected on the same date as the first date of study drug administration are considered to occur before the first dose of study drug administration.

For visits (or events) after randomization, day is calculated as:

- Study day = visit (or event) date - date of randomization + 1

For visits (or events) before randomization, day is calculated as:

- Study day = visit (or event) date - date of randomization

The quantity 'days since first dose' is defined as:

- days since first dose = visit (or event) date – date of first dose + 1

The quantity 'days since last dose' is defined as:

- days since last dose = visit (or event) date - date of last dose

For summaries that present distribution of time expressed in weeks and months, weeks are defined as days divided by seven and months as days divided by 30.4.

5.5.2. Change from Baseline

Change from baseline is calculated using the baseline value (Section 5.4) and the value closest to the target study day, using the rules defined in Section 5.5.3. The 'Safety Population' is defined as all subjects who receive at least one dose of study medication. This population will be used in the assessment and reporting of safety data.

5.5.3. Visit Windows

Analysis visits and their windows are defined using derived study day (Section 5.5.1) instead of relying on visit labels in the clinical database because clinical visits may occur outside protocol-specified windows. Study day and days after last dose are calculated using the actual date of each scheduled and unscheduled assessment and compared to the target for each analysis

visit as specified in Table 3 and Table 4. They are included in analyses of safety and efficacy as follows:

- Efficacy analyses for endpoints assessed through Week 12 use the analysis windows based on target study day in Table 3, irrespective of whether or not a patient is receiving treatment of study drug.
- Efficacy analyses for endpoints assessed after Week 12 use the off-treatment analysis windows based on days after last dose in Table 4.
- Safety analyses use the analysis windows defined in Table 2 so long as the patient is receiving treatment of study drug. Safety and efficacy follow-up at OT Day 35 will also be summarized according to Table 4. Similarly, safety follow-up at OT Day 35 is summarized according to Table 3 for patients completing treatment through Week 12. If a patient permanently discontinues study treatment before Week 12, safety data are summarized according to time since last dose as defined in Table 4.

If a parameter is assessed or measured more than once within a visit window, the one tha.t is closest to the protocol-scheduled time point (i.e., target) is used for the purposes of data analysis and summary. If two assessments are equidistant from a target, the earlier assessment is used. If the visit used for analysis includes two assessments on the same day, the average of the two measurements is used.

Records from visits not closest to the target study day, and therefore not used in analyses, are presented in by-subject data listings.

Majority of the time, the use of nominal visits suffices in a single study. The unscheduled visit can be either be excluded from the summary and included in the listings or only used for assessing the worst result post-baseline. In the above cases, visit windows are not necessary.

Table 3: Analysis Visit Windows for On-Treatment

Analysis Visit	Label	Target		Analysis Window
		Study Day[a]	Days After Last Dose	
0	Day 1[b]	1	-	1
1	Week 1	7	-	2 ≤ study day ≤ 10
2	Week 2	14	-	11 ≤ study day ≤ 21
4	Week 4	28	-	22 ≤ study day ≤ 35
6	Week 6	42	-	36 ≤ study day ≤ 49
8	Week 8	56	-	50 ≤ study day ≤ 70
12	Week 12[c]	84	-	71 ≤ study day ≤ 98 [d]

[a] Study Day is relative to the date of randomization (Section 5.5.1).
[b] Day 1 is the last measurement prior to the first study drug administration.
[c] Week 12 is the end dosing interval.
[d] Data collected 2 or more days after last dose will be excluded from on treatment

5.5.3.1. Off-Treatment Visit Windows

Patients who permanently discontinue study drug prior to Week 12 are asked to resume the planned assessments according to the study schedule in the protocol. Off-treatment values for clinical laboratory evaluations (Section 9.5), vital signs (Section 9.6), and electrocardiograms (Section 9.8) are those that occur after the last dose date for patients permanently discontinuing study drug prior to Week 12 and is summarized relative to their last dose of study drug. Off-treatment safety assessments (clinical labs, vital signs, and electrocardiograms) are grouped for analyses according to the strategy in Table 4.

Table 4: Analysis Visits for Off-Treatment assessments

Off-Treatment Analysis Visit	Label	Target Study Day (days after last dose)	Analysis Window
3	Off Treatment Day 3[b]	3	2 ≤ days after last dose ≤ 4
7	Off Treatment Day 7[b]	7	5 ≤ days after last dose ≤ 10
14	Off Treatment Day 14[b]	14	11 ≤ days after last dose ≤ 17
21	Off Treatment Day 21[b]	21	18 ≤ days after last dose ≤ 24
28	Off Treatment Day 28[b]	28	25 ≤ days after last dose ≤ 31
35	Off Treatment Day 35[b]	35	32 ≤ days after last dose ≤ 38

[a] Last day of on-treatment for patients permanently discontinuing study drug prior or on to Week 12. Assessments that occur on the date of last dose or less than 2 days after last dose are considered on treatment and summarized using Table 3 windows.
[b] The off-treatment values indicate the value closest to the date of last dose.

5.5.4. Laboratory Evaluations Imputations

Any laboratory assessments less than the lower limit of detection (i.e., < LLD) are imputed as LLD/2. If no LLD is available, then the imputed value is the minimum numeric value listed divided by 2 (e.g., < 25 is 25/2=12.5). Laboratory assessments above the ULD are imputed as the ULD. If the lab result is qualitative but presented as > X and X is 10 times greater than the ULN or the ULN is not present, then the value X is used in the analysis.

5.5.5. Estimated Glomerular Filtration Rate (eGFR)

The eGFR is calculated using the formula below according to patient's age at the date of consent. The formula will not change throughout the study. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is used for adult patients (age at consent at least 18 years):

- eGFR (mL/min/1.73 m^2) = 141 × min(S_{cr}/κ, 1)$^{\alpha}$ × max(S_{cr}/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black]

where S_{cr} is serum creatinine (mg/dL), κ is 0.7 for females or 0.9 for males, and α is -0.329 for females or -0.411 for males. Min indicates the minimum of S_{cr}/κ and 1, and max indicates the maximum of S_{cr}/κ and 1. *Age* indicates age at time of serum creatinine collection as collected in CRF.

5.5.5.1. Prognosis of CKD by eGFR and Albuminuria Category

Prognosis of CKD is determined by the intersection of the following eGFR and albuminuria categories (KDIGO 2012):

Table 5: eGFR Category

eGFR Category	eGFR (mL/min/1.73 m^2)
1	≥ 90
2	60 to < 90
3a	45 to < 60
3b	30 to < 45
4	15 to < 30
5	< 15

Table 6: Albuminuria Category

UACR Category	UACR (mg/g)
1	< 30
2	30 to ≤ 300
3	> 300

5.5.6. Urine Albumin to Creatinine Ratio (UACR)

UACR is provided in the central laboratory database as the ratio of urine albumin to urine creatinine from the first morning void (FMV) urine collection. The UACR value is reported in the central laboratory database as missing when the FMV urine albumin result is < LLD. Urine albumin results < LLD and the corresponding UACR missing values are imputed as follows:

- If urine albumin result = < LLD, then
  - Imputed urine albumin result (mg/dL) = LLD/2
  - Imputed UACR(mg/g) = (imputed urine albumin result in mg/dL) / [(urine creatinine in mg/dL) /1000]

The UACR results are log-transformed for analysis to produce data that are more normally distributed. Any imputed UACR result where UACR=0 is considered to be 0.1 mg/g for purposes of calculating the geometric mean.

5.5.6.1. Baseline Urine Albumin to Creatinine Ratio (UACR) Categorical Status

Baseline UACR status will be grouped by the following categories using baseline UACR (see Section 5.4):

- UACR <=300 mg/g
- UACR > 300 mg/g

5.5.6.2. eGFR Category used in Stratification

There will be no multiple baseline eGFR categories used for stratification since the inclusion criteria is as such:

- 20 mL/min/1.73 m^2 < =eGFR < 60 mL/min/1.73 m^2

5.5.6.3. UACR Category used in Stratification (UACR_STRAT)

The UACR category used for stratification (UACR_STRAT) is determined by the randomization list with the following categories:

- UACR <= 300 mg/g
- UACR > 300 mg/g

5.5.7. Electrocardiogram Fridericia Corrected QT Interval

Electrocardiogram intervals are assessed locally at each site. The following formula is used to calculate the QTcF interval for analysis from QT and RR intervals:

- $QTcF = QT/\sqrt[3]{RR}$

where RR = 60 / (Heart Rate).

5.5.8. Natural log(UACR)/eGFR

To evaluate UACR after adjusting for filtration rate, ln(UACR)/eGFR (Sections 5.5.6 and 5.5.5) is assessed.

5.5.9. Trial Duration

Trial duration is used in analyses of efficacy to calculate eGFR slope in the calculation of On-Treatment or Off-Treatment change in eGFR.

Trial duration used in the calculation of change in eGFR in the On-Treatment portion is the Week 12 or End of Treatment if discontinued early analysis visit date minus the date of the baseline assessment plus one.

Trial duration used in the calculation of change in eGFR in the Off-Treatment portion is the Week 17 date minus the date of the baseline assessment plus one. Note, the same baseline value will be used for both On-Treatment and Off-Treatment calculations.

5.5.10. eGFR Slope

The eGFR slope for each patient will be calculated by dividing the change from baseline in eGFR (see Section 5.5.2) by the patient's On-Treatment trial duration (for the Week 12 primary endpoint) or Off-Treatment trial duration (for the Week 17 key secondary endpoint). Calculation of trial duration is described in Section 5.5.9.

5.6. Handling of Missing Data

5.6.1. Missing Efficacy Endpoint Data

5.6.1.1. Missing eGFR for MMRM Analyses

Missing eGFR data are not imputed for the primary, secondary and exploratory endpoint MMRM analysis (Section 7.4.1, 7.5.1 and Section 8.1). A set of sensitivity analyses is included to assess the robustness of conclusions (see Section 7.4.1.1, Section 7.5.1.1 and Section 8.1.1.1.

5.6.1.2. Missing eGFR for ANCOVA Analyses

In the subset of treatment-based multiple imputation sensitivity analyses, missing eGFR data is imputed based on an assumption of missing at random using multiple imputation based on the treatment group to which the patient is assigned. The analysis is performed using the ANCOVA statistical model defined in Section 7.4.1.1. In short, the PROC MI procedure in SAS is used to generate 100 datasets satisfying the assumption of monotone missingness, imputing any missing eGFR values using multiple imputation. Imputation is based on the non-missing observations within each treatment group. Seed specifications used in multiple imputation for sensitivity analyses of the primary endpoint and for sensitivity analyses of exploratory endpoints will be provided.

5.6.1.3. Missing Start and Stop Dates for Concomitant Medications

Missing start dates for concomitant medications are not imputed.

Concomitant medications with incomplete end dates are considered concomitant medications if:

- Day and month are missing, and the year is equal to or after the year of the first date of study drug administration.
- Day is missing and the year is after the year of the first date of study drug administration.
- Day is missing and the year is equal to the year of the first date of study drug administration and the month is equal to or after the month of the first date of study drug administration; or
- Year is missing.

5.6.2. Missing Start and Stop Dates for Adverse Events

Treatment-emergent adverse events (TEAEs) are defined in Section 9.1.

Adverse events with incomplete start dates are considered after the date of first dose, and therefore treatment emergent, if:

- Day and month are missing, and the year is equal to or after the year of the first date of study drug dosing;
- Day is missing and the year is after the year of the first date of study drug dosing;
- Day is missing and the year is equal to the year of the first date of study drug dosing and the month is equal to or after the month of the first date of study drug dosing; or
- Year is missing.

Adverse events with incomplete start dates or end dates are considered on or within 30 days of last dose, if:

- Day, month, and year are missing.
- Day and month are missing, and the year is equal to or before the year of the date of last dose of study drug plus 30 days;
- Day is missing and the year is equal to or before the year of the date of last dose of study drug plus 30 days and month is equal to or before the month of the date of last dose of study drug plus 30 days;

6. STUDY POPULATION

6.1. Subjects Disposition

A disposition summary includes the number and percentage of patients in all analysis populations in the following categories:

Disposition

- ITT population
- Safety population
- Completed treatment through Week 12
  - Week 12 visit in analysis window
  - Week 12 visit out of analysis window
  - Week 12 visit missing
- Discontinued treatment prior to Week 12
  - Reason for discontinuing treatment
- Completed study through Week 17
  - Completed On-treatment and Off-treatment visits
  - Discontinued treatment early but completed in-person study visits
  - Discontinued treatment early but completed by phone
- Terminated from the study before Week 12
  - Reason for study termination
- Terminated from the study before Week 17
  - Reason for study termination
- Completed through Week 17
- Completed treatment through Week 12 and off-treatment assessments through Week 17
- Summaries by study visit
  - On treatment
  - Off treatment
  - In study
  - Stopped study

6.2. Screen Failures

Screen Failures will not be summarized.

6.3. Protocol Deviations

All protocol deviations are listed. Protocol deviations may include excluded medications, patients entering the study despite not satisfying all entry criteria, patients receiving wrong treatment or incorrect dose, or other major protocol deviations.

6.4. Demographic and Baseline Characteristics

Summaries of demographic and other baseline characteristic data are presented by treatment group for all analysis populations. They may also be summarized by select subgroup as appropriate.

The demographic and other baseline characteristics include:

- Baseline Age
- Sex, Race, Ethnicity
- Weight (kg), Height (cm), BMI (kg/m^2)
- Diastolic and systolic blood pressure (mmHg), Heart rate (bpm)
- Serum creatinine
- eGFR, eGFR categorical status (Table 5), (< 30; 30-<45; >=45), (<45; >=45)
- UACR, UACR categorical status (≤ 300; > 300)
- Prognosis of CKD by eGFR and Albuminuria categories (low, moderate, high, very high)
- KDIGO Stratification: CKD progression risk heat map: yellow/orange; red/dark red
- Angiotensin converting enzyme (ACE)-inhibitor treatment and/or Angiotensin II receptor blocker (ARB) (yes/no)
- Kidney Etiologies (Diabetes, Hypertension, and Other.)
- Family History of CKD
- Other baseline variables of interest

6.5. Listing of Subject Inclusion and Exclusion Criteria

A listing of enrolled patients who did not meet inclusion or exclusion criteria is generated.

6.6. Medical History

Medical history is summarized by treatment. Medical history is coded using MedDRA (Medical Dictionary for Regulatory Activities) version 21.1. Medical history items are summarized by MedDRA SOC and PT. A by-patient listing of medical history will be provided.

7. PRIMARY EFFICACY

Analyses of efficacy described in this section are the primary analyses of the efficacy endpoints, and pertain to the ITT population (i.e., all patients randomized in the study), unless otherwise specified. The trial includes endpoints at 12 weeks on-treatment and 5 weeks off-treatment. Additional details regarding the statistical approach and pseudo SAS code are available in the programming conventions document.

The following abbreviations are used in descriptions of the ANCOVA and MMRM analysis models:

Table 7: Model Parameter Abbreviations

Abbreviation	Model Term
HEAT_STRAT	KDIGO heat map stratification (stratum 1 and 2)
TRT	treatment group
VISIT	analysis visit used as time
TRT x VISIT	the interaction between treatment and time

7.1. General Considerations

Results will not be presented by individual study centers. Analyses are performed for all bardoxolone methyl patients in comparison with all placebo patients. Summary statistics for observed values, change from baseline, and percent change from baseline are presented by randomized treatment group. Missing values are handled as described in Section 5.6.

7.2. Statement of the Null and Alternate Hypothesis

The primary efficacy analysis compares the change from baseline in eGFR for patients randomized to bardoxolone methyl (μ BARD) to the change from baseline in eGFR for patients randomized to placebo (μ placebo) at the endpoint-specified visit according to the following hypotheses:

- Null hypothesis, H0: (μ BARD) – (μ placebo) = 0 mL/min/1.73 m2
- Alternative hypothesis, H1: (μ BARD) – (μ placebo) ≠ 0 mL/min/1.73 m2

Because eGFR decreases with disease progression, an increase in eGFR relative to placebo is considered evidence of benefit.

7.3. Subgroup Analysis

The off-treatment efficacy endpoints, the primary efficacy endpoint and secondary efficacy endpoint, will be descriptively analyzed for subgroups of interest to assess the general consistency of results across subgroups.

The following subgroup analyses are tabulated:

- Sex: female; male
- Ethnicity: Non-Hispanic/Latino; Hispanic/Latino
- Race: White; Non-White
- Baseline BMI (kg/m^2): < 30; ≥ 30
- Baseline eGFR ($mL/min/1.73\ m^2$): < 30; 30-<45; >=45
- Baseline eGFR (mL/min/1.73 m2): <45; >=45
- Baseline UACR (mg/g): ≤ 300; > 300
- Family history of CKD: Yes; No
- Kidney Etiologies (Diabetes, Hypertension, and Other)
- KDIGO Stratification: CKD progression risk heat map: yellow/orange; red/dark red
- Patients with IP Interruptions (Yes/No)

Subgroup analyses will include nominal significance levels for descriptive purposes only. The model used for subgroup analyses is the same as the primary analyses (Section 7) with additional terms of subgroup and subgroup-by-treatment.

7.4. Primary Efficacy Endpoint

7.4.1. Primary Analysis of the Primary Endpoint

The primary endpoint of this study is the change in eGFR at Week 12. The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at Week 12 using mixed models repeated measures (MMRM) analysis with the following fixed factors: KDIGO strata (HEAT_STRAT), treatment group (TRT), time (i.e., VISIT; analysis visit number), and the interaction between treatment and time (TRT x VISIT).

The trial design separates discontinuation of study drug from discontinuation of study follow-up. Therefore, patients may discontinue early from study drug while continuing follow-up with study visits and assessments. The primary analysis of eGFR at Week 12 uses available eGFR values irrespective of whether a patient is receiving treatment. The MMRM analysis uses all eGFR values collected through Week 12 according to analysis visits 1,2,4,6,8, and 12 (Section 5.5.3). An unstructured covariance matrix is used.

In the event the MMRM model with an unstructured covariance structure does not converge, the following covariance structures are substituted, in the order listed. Each subsequent covariance structure is used only if each previous covariance structure is used and no previous model converged.

1. Heterogeneous Toeplitz covariance structure (assuming different variances at each time point and that measurements taken closer together in time are more highly correlated than those taken farther apart).

2. Toeplitz covariance structure (assuming measurements taken closer together in time are more highly correlated than those taken farther apart).
3. First order auto-regressive [AR(1)] covariance structure (assuming measurements taken closer together in time are more highly correlated than those taken farther apart, but the correlation is more constrained than the Toeplitz structure).
4. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time they were taken). A compound symmetry covariance structure was assumed in the sample size calculation.

If the MMRM model does not converge using any of the aforementioned covariance structures, variables from the model statement may be removed.

The difference between bardoxolone methyl and placebo in change from baseline of eGFR is estimated along with the 95% confidence interval at Week 12 for the primary analysis of the primary endpoint.

7.4.1.1. Sensitivity Analysis of the Primary Endpoint – No Imputation for Missing Data

The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at Week 12 using ANCOVA analysis with the following fixed factors: KDIGO strata (HEAT_STRAT) and treatment group (TRT).

The ANCOVA analysis uses eGFR values collected in the Week 12 analysis window (Table 3). Missing Week 12 eGFR data are not imputed.

The difference between bardoxolone methyl and placebo in change from baseline of eGFR is estimated along with the 95% confidence interval at Week 12.

7.4.1.2. Sensitivity Analysis of the Primary Endpoint – Imputation for Missing Data

The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at Week 12 using ANCOVA analysis with the following fixed factors: KDIGO strata (HEAT_STRAT) and treatment group (TRT).

The ANCOVA analysis uses eGFR values collected in the Week 12 analysis window (Table 3). For one analysis, Missing Week 12 eGFR data are imputed according to Section 5.6.1.2.

The difference between bardoxolone methyl and placebo in change from baseline of eGFR is estimated along with the 95% confidence interval at Week 12.

7.5. Secondary Efficacy Endpoint

7.5.1. Primary Analysis of the Secondary Endpoint

The secondary endpoint of this study is the change in eGFR at Week 12 by CKD etiologies (Diabetes, Hypertension, and Other). The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at Week 12 by CKD etiology using mixed models repeated measures (MMRM) analysis as defined in Section 7.4.1.

7.5.1.1. Sensitivity Analysis of the Secondary Endpoint

Sensitivity analysis of the secondary endpoint by treatment group and etiology is run according to Section 7.4.1.1.

8. EXPLORATORY EFFICACY

The following data summaries and analyses are presented for the ITT analysis set. Additional sensitivity analyses may be performed as appropriate.

All data values within the appropriate visit windows contribute to the analysis.

All analyses use ITT population.

8.1. Exploratory Efficacy Endpoint

8.1.1. Off-Treatment MMRM eGFR Analysis

The exploratory endpoint of this study is the change in eGFR at Day 3, 7, 14, 21, 28, and 35 during the Off-Treatment portion of the study. The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at Day 3, 7, 14, 21, 28, and 35 using mixed models repeated measures (MMRM) analysis with the following fixed factors: KDIGO strata (HEAT_STRAT), treatment group (TRT), time (i.e., VISIT; analysis visit number), and the interaction between treatment and time (TRT x VISIT).

The MMRM analysis uses all eGFR values collected from Week 12 to Week 17 according to off-treatment analysis visits 3,7,14,21,28, and 35 (Section 5.5.3.1). An unstructured covariance matrix is used. Baseline value is original On-Treatment baseline value.

1. In the event the MMRM model with an unstructured covariance structure does not converge, the covariance structures are substituted as defined in Section 7.4.1.

8.1.1.1. Sensitivity Analysis of Off-Treatment eGFR analysis – No Imputation for Missing Data

The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo using ANCOVA analysis with the following fixed factors: KDIGO strata (HEAT_STRAT) and treatment group (TRT).

The ANCOVA analysis uses eGFR values collected in each off-treatment visit (3,7,14,21,28, and 35) analysis window (Table 4). Missing eGFR data per visit are not imputed.

The difference between bardoxolone methyl and placebo in change from baseline of eGFR is estimated along with the 95% confidence interval at each off-treatment visit (3,7,14,21,28, and 35).

8.1.1.2. Sensitivity Analysis of Off-Treatment eGFR Analysis – Imputation for Missing Data

The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo using ANCOVA analysis with the following fixed factors: KDIGO strata (HEAT_STRAT) and treatment group (TRT).

The ANCOVA analysis uses eGFR values collected in each off-treatment visit (3,7,14,21,28, and 35) analysis window (Table 4). For one analysis, Missing eGFR data per off-treatment visit are imputed according to Section 5.6.1.2.

The difference between bardoxolone methyl and placebo in change from baseline of eGFR is estimated along with the 95% confidence interval at each off-treatment visit (3,7,14,21,28, and 35).

8.1.1.3. Off-Treatment MMRM eGFR Analysis for Week 12 and Week 17 Completers

Analyses will be conducted as described in Section 8.1.1 for patients who have completed 12 weeks of treatment and have off-treatment eGFR values collected within each of the analysis visit windows through Week 17 (Table 4).

8.1.1.4. Off-Treatment ANCOVA eGFR Analysis for Week 12 and Week 17 Completers

Analyses will be conducted as described in Section 8.1.1.1 for patients who have completed 12 weeks of treatment and have off-treatment eGFR values collected within each of the analysis visit windows through Week 17 (Table 4).

8.1.1.5. Off-Treatment Non-linear Mixed Model

A series of nonlinear mixed models will be used to fit the off-treatment eGFR change from baseline results for the Bardoxolone Methyl treated subjects. The modelling is to examine the behavior of eGFR among treated subjects once treatment is discontinued. Initially, the following model will be fit to the data:

$$Y_{ij} = \beta_{0i} + \beta_{1i} * exp(\beta_{2i} * t_{ij}) + e_i,$$

where Y_{ij} denote the eGFR value for the i^{th} subject at the j^{th} timepoint, β_{0i} is the asymptote, β_{1i} is referred to as the amount, β_{2i} is referred to as the decay rate, t_{ij} denotes the time for the i^{th} subject at the j^{th} timepoint, and e_i denotes the error term. In the model where all effects are fixed, the βs are defined as follows:

- $\beta_{0i} = \beta_0$
- $\beta_{1i} = \beta_1$
- $\beta_{2i} = \beta_2$

The random effects are introduced into a sequence of models as described below:

1) First a random effect for β_{0i} will be introduced and defined as $\beta_{0i} + U_{oi}$, where U_{oi} is the random effect.
2) The second model to be fit will include a random effect for both β_{0i} and β_{1i}, with the random effect for β_{1i} is defined as $\beta_{1i} + U_{1i}$.
3) The third model to be fit will include a random effect for all three coefficients, with the random effect defined as $\beta_{2i} + U_{2i}$.

Each additional random effect will be added to the model if the model is stable. The Akaike information criteria will be used to select the final model (lower is better). If none of the non-linear mixed models converge, other models may be implemented such as a quadratic model.

8.1.2. [redacted]

[redacted]

9. SAFETY AND TOLERABILITY

Safety and tolerability are evaluated by AEs, SAEs, clinical laboratory test results, body weight, vital signs, 12-lead ECG findings, and physical examination. All analyses of the safety data are performed using the safety analysis set. Descriptive statistics are presented by treatment group assignment in the safety analysis set. No formal statistical testing is performed for safety analyses. Safety is also summarized by a portion of the subgroups defined in Section 7.3. On-treatment values are summarized according to the analysis study windows in Section 5.5.3; off-treatment values are summarized according to the analysis study windows in Section 5.5.3.1. Safety data summaries are grouped by treatment.

Continuous safety parameters (including selected clinical chemistries and vital signs) may be summarized using the methodology described in Section 9.5.1 and Section 9.6. Only the visit windows outlined in Section 5.5.1 are included in these analyses.

9.1. Adverse Event Preferred Term and Body/Organ System Summary Tables

Treatment-emergent adverse events (TEAEs) are summarized by treatment as defined by the safety analysis set.

Treatment-emergent adverse events (TEAEs) are events that either:

- Have a date of onset on or after the date of first dose and not more than 30 days after the date of the last dose of study drug, or
- Have no recorded date of onset with a stop date after the first dose of study drug, or
- Have no recorded date of onset or stop date.

General considerations for TEAE summaries are:

- Multiple events by preferred term (PT) and system organ class (SOC) are counted once only per patient for summaries of TEAE incidence.
- For summaries of TEAE incidence by severity, only the most severe event is counted per patient.
- For summaries of TEAE incidence by relationship, only the most related event is counted per patient.
- A TEAE with a missing resolution date or incomplete date that is not identified as continuing is assumed to be continuing.
- For summaries of the number of TEAE events, all TEAEs are counted.
- Withdrawal TEAEs include the subset of TEAEs that started one to 30 days after the last dose of study drug.

Off-treatment AEs are events with a start date more than 30 days after last dose and not considered treatment emergent. Off-treatment AEs will be summarized separately.

AEs are coded using MedDRA (Medical Dictionary for Regulatory Activities) version 21.1. In MedDRA, each verbatim term is mapped to a preferred term and high level term (HLT), which is then mapped to a system organ class (SOC).

The investigator grades the severity of the AEs as mild, moderate, or severe as defined in the study protocol. The investigator grades association or relatedness to the study medication according to criteria specified in Section 11.4 of the protocol.

As defined in the protocol, a serious adverse event (SAE) is an adverse event (occurring at any dose and regardless of causality) that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect in an offspring of a patient taking study drug;
- Is an important medical event.

9.1.1. Missing and Partial AE Onset Dates

Rules for handling missing or partial AE Onset Dates are included in Section 5.6.2.

9.1.2. Summaries of Adverse Events

TEAEs and OTAEs are summarized by treatment based on year of AE onset and overall. For each treatment, SOC, and PT, the number and percentage of patients reporting an event is calculated. In summary tables, SOC is presented alphabetically and events within each SOC are presented by decreasing frequency count.

Summary tables (number and percentage of patients and events) of TEAEs (by SOC and PT) are provided by treatment as follows:

- All TEAEs
- All related TEAEs (definitely, probably, or possibly related)
- All TEAEs by severity
- All serious TEAEs (including deaths)
- All non-serious TEAEs
- All related serious AEs (including deaths)
- All TEAEs leading to permanent discontinuation of study drug
- TEAEs by time to onset (≤ 12 weeks and >12 weeks)
- TEAEs exhibited in >5% of patients

Listings are provided showing:

- All AEs
- Deaths
- Serious adverse events
- AEs leading to permanent discontinuation of study drug
- AEs leading to de-escalation of study drug

9.2. Exposure and Compliance

The duration of study drug exposure is defined as the number of days on treatment from the first dose of study drug until the last dose of study drug (last dose – first dose + 1). Study drug exposure is summarized by descriptive statistics. Summaries include the total dose (mg) received (based on the number of pills returned), study drug compliance, and duration (days) of exposure during the study treatment period. In addition, a summary of the number and percentage of patients exposed by dose (placebo, 5 mg, 10 mg, 20 mg, 30 mg) and by visit is generated. If a patient received more than one dose during a visit window, the duration of the longest dose is used to calculate exposure. Summaries of the number and percentage of patients exposed by dose include subgroup analyses by baseline UACR (UACR $\leq$ 300 mg/g vs. UACR > 300 mg/g).

Total number of doses dispensed and total dose (mg) dispensed is calculated from total number of kits (bottles) recorded on the Study Drug Dispensation eCRF. Total number of doses received is calculated from information on the eCRF of Study Drug Return and Study Drug Dispensation, as the (total number of doses dispensed – total number of doses returned). If a kit is not returned but the patient had a subsequent dispensation, then the non-returned kit is assumed to have been taken in full. However, if a kit is not returned and no kit is subsequently dispensed, then the non-returned kit is assumed to not have been taken. Study drug compliance (%) is calculated as 100 × total number of doses received / total number of study days of study participation, excluding the off-treatment period.

Patients not at per-protocol dose are listed including reasons.

9.3. Concomitant Medications

Concomitant medications are coded using the World Health Organization (WHO) drug dictionary (Enhanced version, March 2019, B3 format) for anatomical therapeutic chemical classification (ATC) and preferred drug name. A patient who used multiple medications is counted only once for each ATC and preferred drug name. ATC and preferred drug name within each ATC are sorted alphabetically. Coded concomitant medications are summarized by treatment by WHO ATC class and preferred name. A patient who used multiple medications is counted only once for each ATC and preferred drug name. Percentages are based on the number of patients in the safety analysis set. Each summary is ordered by descending order of incidence of ATC class and preferred name within each ATC class. Concomitant medications will be summarized by treatment year and overall.

A concomitant medication is any medication taken at the time of first study treatment or a medication that was started after the start of study drug dosing. Specifically, concomitant medications are medications

- that are continued from screening and continued after the first study drug dosing, or
- that have start dates or stop dates within the treatment period, or
- that have no end date.

Medications with an end date on the date of first study drug administration are not considered concomitant medications.

Patients who take excluded medications (defined in the Protocol Section 9.3.1) during the study are listed.

9.3.1. Missing and Partial Concomitant and Other Medication Start and Stop Dates

Missing and partial concomitant medication start and stop dates are detailed in Section 5.6.1.3.

9.4. Prior and Concomitant Procedures and Surgeries

Prior and concomitant procedures and surgeries are listed.

9.5. Clinical Laboratory Evaluations

Laboratory data are summarized at baseline and at each time point by treatment.

9.5.1. Continuous Summaries of Laboratory Results

Laboratory evaluations and change from baseline are summarized by treatment, laboratory category (hematology, chemistry, urinalysis and microscopy), test, and study visit using continuous statistics. The estimated glomerular filtration rate (eGFR) results are calculated using formulas described in Section 5.5.5.

The change from baseline in select laboratory evaluations at the protocol-defined on treatment endpoint time points (i.e., Week 1,2,4,6,8, and 12) for patients treated with bardoxolone methyl compared to placebo may be performed using MMRM model described in Section 7.4 and the ANCOVA sensitivity analysis described in Section 7.4.1.1.

The change from baseline in select laboratory evaluations at the protocol-defined off treatment endpoint time points (i.e., Day 0,3,7,14,21,28, and 35) for patients treated with bardoxolone methyl compared to placebo may be performed using MMRM model described in Section 8.1.

Box plots and line graphs are generated for selected laboratory test results, such as eGFR, UACR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, BNP, BUN, uric acid, magnesium, creatinine, and creatine kinase (CK). Line graphs include mean ± SE over time for both the observed values and for change from baseline.

Summaries of continuous statistics are provided for the following urinalysis parameters: albumin, creatinine, pH, erythrocytes, and specific gravity. Qualitative lab results are included in the listings but are not summarized. Laboratory results that are above or below normal limits are flagged in the listings.

Summaries of UACR (Section 5.5.6) will use the geometric mean (with standard error) with 95% confidence intervals instead of the arithmetic mean and will display UACR results in original units of mg/g. Changes from baseline in UACR are calculated as the ratio of each visit to baseline and reported as the post-baseline/baseline ratios and are summarized by geometric means with 95% confidence intervals at each time point. Similar On Treatment MMRM analyses as described in Section 7.4.1 and the ANCOVA analysis described in Section 7.4.1.1. will be performed for UACR ratio to baseline. The change from baseline for UACR ration to baseline at the protocol-defined endpoint time points Week 17 for patients treated with bardoxolone methyl compared to placebo may be performed using the ANCOVA models described in Section 7.4.1.1 and Section 8.1.1.1. Additionally, UACR is summarized by baseline UACR quartile. Summaries of UACR include values for scheduled visits.

9.5.1.1. Natural log(UACR)/eGFR

Mean ratios of natural log(UACR)/eGFR (Section 5.5.8) are summarized at each time point. The ratio of natural log(UACR)/eGFR by analysis visit is summarized by arithmetic means.

9.5.2. Categorical Summaries of Laboratory Results

Select laboratory parameters will be summarized using shift tables. Shift tables are summarized by treatment, laboratory category (hematology, chemistry, urinalysis, and microscopy), and laboratory test and present shifts from baseline status (Normal, Low, High) to worst on study treatment status (Normal, Low, High). The worst abnormality values are defined as the maximum values while on study treatment, with the exception of magnesium and hemoglobin. The worst abnormal values for magnesium and hemoglobin are defined as the minimum values while on study treatment.

Additionally, laboratory parameters of specific interest (ALT, AST, UACR) are summarized using shift tables that summarize shifts from (1) baseline status to end of treatment status, (2) worst on-treatment status to worst off-treatment status (3) worst on-treatment status to Day 35 off-treatment status, and (4) baseline status to worst on-treatment status (5) baseline to worst off-treatment, and (6) worst on-treatment status to best (lowest) off-treatment status. The number and percentage of patients are summarized. For UACR, summaries will present shifts from/to the categories listed in Section 5.5.6.1. For ALT and AST, summaries will present shifts from/to the following categories:

- $\leq$ ULN
- > ULN to $\leq$ 3x ULN
- > 3x ULN

In addition, a summary table is provided for the number and percentage of patients meeting the following threshold levels at any time during the study:

- > 5x ULN for more than 2 weeks
- > 3x ULN and (TBL > 2x ULN or INR > 1.5)
- > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

- BNP > 200 pg/mL
- Magnesium < 1.3 mEq/L (0.65 mmol/L)
- NT-proBNP > 1000 pg/mL

9.5.2.1. Transaminase

Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots are generated for ALT and AST versus TBL.

A listing of subjects with abnormal ALT, AST, or TBL will also be provided.

9.6. Vital Signs

Vital signs assessments will include weight (kg) and also include other measurements such as blood pressure and temperature. When three blood pressure measurements are taken, the average of the second and third results will be used for the given visit.

9.6.1. Body Weight

Body weight, as collected during each in-office visit, is summarized using descriptive statistics for observed results and change from baseline at time point. In addition, number and percentage of patients experiencing a five pound (2.3 kilogram) or greater increase in weight are summarized by time point. Boxplots and line graphs of change from baseline over time for weight are plotted.

9.7. Physical Examination

Physical exam results are listed.

9.8. Electrocardiogram

Electrocardiogram (ECG) data, such as clinical interpretation of ECGs, heart rate and interval assessments of PR, QRS, and QT are collected on the eCRF. QTcF is calculated for analysis (Section 5.5.7). Descriptive statistics for observed values and change from baseline at each time point are presented for these 12-lead ECG interval assessments. In addition, number and percentage of patients with any abnormal values (i.e., above a pre-specified threshold) at any time during the study are summarized by time point and overall. The pre-specified levels of ECG QTc thresholds (Table 8) are consistent with FDA guidance:

Table 8: Pre-Specified Threshold Levels for ECG Parameters

ECG Parameter	Pre-Specified Level
PR	> 200 msec
QTcF	> 450 and ≤ 480 msec
	> 480 and ≤ 500 msec
	> 500

ECG Parameter	Pre-Specified Level
	Change from baseline: >30 and ≤ 60 msec
	Change from baseline: > 60 msec
Heart rate	< 40 beats/min
	> 100 beats/minTable

Boxplots and line graphs of change from baseline over time for ECG parameters are plotted.

9.9. Pregnancy

A listing is provided for serum and urine pregnancy results of all on-study pregnancies.

10. PHARMACOKINETICS

Pharmacokinetic concentration data will be listed. Draws will begin on Week 12. A separate document contains details regarding other planned pharmacokinetic analyses.

11. COVID-19 IMPACT

11.1. Operational Impact

The COVID-19 pandemic has impacted the conduct of the study per protocol. To minimize study disruptions, alternative drug dispensation methods and remote visit completion methods are available if it is inadvisable for a patient to be seen for an in-person clinic visit or if a patient is unwilling to come to the clinic. Any study procedures that cannot be conducted remotely will be noted as missing.

Sites should record if visits, data collection, drug dispensation, and drug administration are impacted by or related to COVID-19.

The number and percentage of patients are summarized by visit and treatment group for the following categories:

- Visit impact by COVID-19
  - Visit not done
  - Visit conducted out of window
  - One or more procedures could not be performed
- Alternative data collection methods
  - No change (occurred as expected per protocol)
  - Telephone visit
  - Video conference visit
  - Home health care visit
  - Local lab
  - Other
- Drug dispensation impact
  - No change (office visit)
  - IP dispense not scheduled (telephone visit)
  - Mailed to patient
  - Home health care provided
  - Dose not escalated
  - Dose de-escalated
  - Other

The number and percentage of patients are summarized treatment group for Drug Interruption due to COVID-19:

- Tested positive for COVID-19 (yes, no, not tested)
- Primary reason for interruption (medical monitor/sponsor recommendation, site mandate, patient choice, insufficient IP supply, other)

A by-patient listing of all study visits that were affected due to COVID-19 including a description of how the patient's participation was altered will be provided.

Early discontinuations of study drug or study due to COVID-19 will be summarized and listed in disposition summary tables and the disposition listing (described in Section 6.1), respectively.

All deviations due to the impacts of COVID-19 will be identified and documented accordingly by the site and the Sponsor. The failure to complete a protocol visit will not be considered as a reason for study discontinuation and will not be considered as a major deviation. All COVID-19-related deviations will be identified in the protocol deviation listing (Section 6.3).

11.2. Impact on Efficacy

The primary and key secondary endpoints, as well as the secondary endpoints are lab-based endpoints (i.e, change in eGFR). Home health care visits and/or local laboratories are available to collect safety labs, including eGFR, for patients who are unable or unwilling to come for in-clinic visits. Central laboratory kits are utilized at in-clinic visits, home health care visits, and local laboratory visits. Therefore, the contingency measures put in place to collect this critical efficacy data are not expected to impact the efficacy results. Missing data due to COVID-19 is handled as described in Section 5.6.

Sensitivity analyses may be performed as appropriate to assess the potential impact of the COVID-19 pandemic on the treatment effect on efficacy outcomes.

11.3. Impact on Safety

Patient narratives will be provided for all patients who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19.

For patients who are unable to complete an in-clinic visit, safety assessments can be performed through alternative remote visit methods. Central laboratory kits are used to assess safety laboratory information regardless of visit method; therefore, the contingency measures put in place to collect this critical safety data are not expected to impact the safety laboratory results.

Subgroup analyses may be performed as appropriate to assess the potential impact of the COVID-19 pandemic on the treatment effect on safety outcomes.

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13. APPENDIX

13.1. SAP Change Summary

SAP Revision Chronology:			
Version	Date	Changes	Main Rationale
SAP version 1	10-JUN-2021	Original	N/A
SAP version 2 (Amendment 1)	06-OCT-2021	• Updated COVID requirements for summarization • Removed In-clinic/Phone visits categories from the disposition by visit summary • Protocol Deviation classification by blinded team removed • Added Non-linear modelling of Off-Treatment eGFR results and/or change from baseline in the Bardoxolone Methyl treated subjects • Added All non-serious TEAE summarization • Added additional lab threshold levels to summarize	Additional Analysis

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